

What is claimed is :

1. A novel HIV receptor, named the V3 loop HIV receptor, comprising at least  
5 one protein choosen among P95/nucleolin, P40/PHAPIII and P30/PHAPI  
proteins.

*Sud 71*  
10 2. A peptidic or non peptidic inhibitor molecule that is able to modify the  
interaction between, on one hand the V3 loop receptor according to claim 1  
present at the cell surface of a patient infected with a human HIV retrovirus,  
specifically HIV-1 or HIV-2, and on the other hand the gp120 envelope  
glycoprotein of said HIV retrovirus.

15 3. The inhibitor molecule according to claim 2 which comprises a peptide  
fragment of P95/nucleolin, P40/PHAPII or P30/PHAPI or its pseudopeptide  
counterpart.

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20 4. The inhibitor molecule of claim 2 which consists in a peptide or pseudopeptide  
which is homologous containing one or several aminoacid additions, deletions  
and/or substitutions in the aminoacid sequence of the inhibitor molecules  
according to claim 3.

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25 5. The inhibitor molecule according to anyone of claims 1 to 4 in which the -  
CONH- peptide bound is modified and replaced by a (CH<sub>2</sub>NH) reduced bound, a  
(NHCO) retro inverso bound, a (CH<sub>2</sub>-O) methylene-oxy bound, a (CH<sub>2</sub>-S)  
thiomethylene bound, a (CH<sub>2</sub>CH<sub>2</sub>) carba bound, a (CO-CH<sub>2</sub>) cetomethylene  
bound, a (CHOH-CH<sub>2</sub>) hydroxyethylene bound), a (N-N) bound, a E-alcene  
bound or also a -CH=CH- bound.

6. The inhibitor molecule according to anyone of claims 1 to 5, which is derived from the P95/nucleolin aminoacid sequence and choosen among the following sequences :

- 5       - the sequence beginning at the aminoacid in position 22 and ending at the aminoacid in position 44;
- the sequence beginning at the aminoacid in position 143 and ending at the aminoacid in position 171;
- 10       - the sequence beginning at the aminoacid in position 185 and ending at the aminoacid in position 209;
- the sequence beginning at the aminoacid in position 234 and ending at the aminoacid in position 271;

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cont

15       7. The inhibitor molecule according to anyone of claims 1 to 5, which is derived from the P30/PHAPI aminoacid sequence and choosen among the following sequences :

- the sequence beginning at the aminoacid in position 168 and ending at the aminoacid in position 182;
- 20       - the sequence beginning at the aminoacid in position 187 and ending at the aminoacid in position 222;
- the sequence beginning at the aminoacid in position 240 and ending at the aminoacid in position 249; it being understood that the proximity of the two first sequences and the two last sequences allow one of ordinary skill in the art to gather the sequences contained in two sets of sequences as follows :
- 25       - the sequence beginning at the aminoacid in position 168 and ending at the aminoacid in position 222;
- the sequence beginning at the aminoacid in position 187 and ending at the aminoacid in position 249;

8. The inhibitor molecule according to anyone of claims 1 to 5, which is the following sequence derived from the P40/PHAPII aminoacid sequence :

- the sequence beginning at the aminoacid in position 223 and ending at the aminoacid in position 277

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9. The inhibitor molecule according to claim 2 which comprises a polymer of an inhibitor molecule according to anyone of claims 3 to 8, that contains 2 to 20 monomer units of the aminoacid sequence of interest derived from the aminoacid sequence of either P95/nucleolin, P40/PHAPIII and P30/PHAPI, preferably 4 to 15 monomer units and more preferably 5 to 10 monomer units.

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~~10. The inhibitor molecule according to anyone of claims 1 to 9 which is under the form of a MAP matrix structure.~~

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11. The inhibitor molecule according to claim 2 which consists in a monoclonal or polyclonal antibody directed against the P95/nucleolin, P40/PHAPII and P30/PHAPI protein.

20 12. The inhibitor molecule according to claim 2 which consists in a polyclonal or monoclonal anti-idiotypic antibody that mimicks the V3 loop peptide of the HIV gp120 glycoprotein.

Sub 25 13. A therapeutic composition comprising a pharmaceutically effective amount of an inhibitor molecule according to anyone of claims 1 to 12, optionally in combination with another anti-HIV molecule such as AZT.

Sub 27 14. A therapeutic composition comprising a pharmaceutically effective amount of

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a polynucleotide a polynucleotide coding for the P95/nucleolin, P40/PHAPIII and P30/PHAPI or one of the monomeric or oligomeric peptide inhibitor molecules according to anyone of claims 2 to 9.

- 5 15. A method of altering the expression of the V3 loop HIV receptor of claim 1 in an individual, which comprises the step of introducing a defect copy of two genes among the genes coding for P95/nucleolin, P40/PHAPIII and P30/PHAPI protein and more preferably a defect copy of the three genes coding for P95/nucleolin, P40/PHAPIII and P30/PHAPI protein in the cells of the individual.

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16. A method for specific replacement, in particular by targeting the P95/nucleolin, P40/PHAPIII and P30/PHAPI protein encoding DNA, called insertion DNA, comprising all or part of the DNA structurally encoding for the P95/nucleolin, P40/PHAPIII and P30/PHAPI protein or one of its biologically  
15 active derivatives, when it is recombined with a complementing DNA in order to supply a complete recombinant gene in the genome of the host cell of the patient, characterized in that :

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- the site of insertion is located in a selected gene, called the recipient gene, containing the complementing DNA encoding the P95/nucleolin, P40/PHAPIII and P30/PHAPI protein or one of its biologically active derivatives and in that

- the polynucleotide coding for the P95/nucleolin, P40/PHAPIII and P30/PHAPI protein or one of its biologically active derivatives may comprise:

- 25 - « flanking sequences » on either side of the DNA to be inserted, respectively homologous to two genomic sequences which are adjacent to the desired insertion site in the recipient gene.  
- the insertion DNA being heterologous with respect to the recipient gene,

and

- the flanking sequences being selected from those which constitute the above-mentioned complementing DNA and which allow, as a result of homologous recombination with corresponding sequences in the recipient gene, the reconstitution of a complete recombinant gene in the genome of the eukaryotic cell.

17. A therapeutic composition comprising an antisense polynucleotide complementary to the nucleic sequence of P95/nucleolin, P40/PHAPIII and P30/PHAPI represented in Figure 49.

18. A method for screening inhibitor molecules according to any one of claims 1 to 12 comprising the steps of:

a) Preparing a complex between the P95/nucleolin, P40/PHAPII and P30/PHAPI protein and a ligand that binds to the P95/nucleolin, P40/PHAPII and P30/PHAPI protein by bringing into contact the purified P95/nucleolin, P40/PHAPII and P30/PHAPI protein with a solution containing a molecule to be tested as a ligand binding to the P95/nucleolin, P40/PHAPII and P30/PHAPI protein;

b) visualizing the complex formed between the purified P95/nucleolin, P40/PHAPII and P30/PHAPI protein and the molecule to be tested.

19. A method for screening molecules that modulate the expression of the P95/nucleolin, P40/PHAPII and P30/PHAPI protein, comprising the steps of:

a) cultivating a prokaryotic or an eukaryotic cell that has been transfected with a nucleotide sequence encoding the P95/nucleolin, P40/PHAPII and P30/PHAPI protein, placed under the control of its own promoter;

b) bringing into contact the cultivated cell with a molecule to be tested;

c) quantifying the expression of the P95/nucleolin, P40/PHAPII and P30/PHAPI protein.

20. A method for screening the normal expression of the V3 loop HIV receptor  
5 according to the invention comprising the steps of :

a) making use of monoclonal or polyclonal antibodies directed either to the whole receptor or to the P95/nucleolin, P40/PHAPII and P30/PHAPI protein on isolated patient cells, specifically peripheral mononuclear cells (PMC), said antibodies being optionally radioactively or non radioactively labeled

10 b) detecting the bound antibodies onto said patients cells.

21. A diagnostic method for detecting mutations in the gene coding for P95/nucleolin, P40/PHAPII or P30/PHAPI comprising the steps of :

a) amplifying the full coding region of P95/nucleolin, P40/PHAPII or P30/PHAPI  
15 from a patient using a pair of specific primers;


b) determining the sequence of the amplified DNA;

c) comparing the sequence obtained at step b) with the nucleic sequences of P95/nucleolin, P40/PHAPII or P30/PHAPI reported in Figure 49.

20 22. A diagnostic nucleic probe comprising at least 20 nucleotides of a mutated sequence of P95/nucleolin, P40/PHAPII or P30/PHAPI, said probe containing at least one specific mutation identified according to the method of claim 21.

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25 23. A method for screening inhibitor according to anyone of claims 2 to 12, comprising the following steps :

a) bringing into contact cells expressing the novel receptor according to the present invention at their surface with an amount of a HIV retrovirus equalling to the TCID<sub>50</sub>;

- b) incubating said cells and retroviruses at 37°C during a period of time sufficient to allow the entry of the retrovirus within the cells, in the presence of a defined amount of the compound to be assayed;
- c) washing the cells in order to remove the retroviruses that has been absorbed
- 5 onto the membranes of the cells;
- d) treating the cells in order to eliminate the remaining extracellular retroviruses, for example by a controlled proteolysis with trypsin;
-  e) preparing cytoplasmic extracts by treating the cells of step d) with an extraction buffer, for example with a buffer containing 20 mM Tris-HCl (pH7.6),
- 10 0.15 M NaCl, 5 mM Mg Cl<sub>2</sub>, 0.2 mM PMSF, 100 U/ml aprotinin and 0.5% Triton X-100;
- f) centrifugating the cells obtained at step c), for example at 1000 g, and harvesting the supernatant medium, in order to separate the retroviral proteins;
- g) detecting and optionally measuring the concentration of the HIV proteins,
- 15 either directly or indirectly, for example by steric hindering..

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